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Developments in the drug treatment of schizophrenia

Gavin P. Reynolds

Despite its efficacy in many cases, the drug treatment of schizophrenia remains problematic. A substantial proportion of patients do not improve, and many others suffer from unpleasant side-effects. In this review, Gavin Reynolds *describes the new approaches to antipsychotic drug development that attempt to address these problems, and relates some of these approaches to growing evidence for neuronal pathology in the brain in schizophrenia.*

The past few years have been an exciting time for research into schizophrenia. Convincing evidence has emerged for a neuropathology of the disease, with an emphasis on neuronal deficits in certain regions of the temporal lobe and, to a lesser extent, abnormalities in the frontal cortex (see Box 1). Changes have also been identified in pre- and post-synaptic markers of certain neurotransmitter systems that might reflect this neuropathology. At the same time there have been substantial neuropharmacological developments that have led to the identification of potential antipsychotic drugs. While some members of this new generation of drugs have a clearly established parentage, others reflect totally new approaches to the treatment of psychosis. So far, however, there has been very little convergence between these pathological and psychopharmacological advances.

The history of modern antipsychotics began in the early 1950s with the introduction of chlorpromazine, the first treatment with a specific action on schizophrenic symptoms. This action was found to occur in conjunction with deleterious side-effects, most notably parkinsonism, dyskinesias and akathisia. These extrapyramidal symptoms were then considered by some to be a necessary concomitant to the antipsychotic efficacy of these drugs, and led to the drugs being described as 'neuroleptic'. Over the subsequent two decades a number of other effective antipsychotic drugs were developed, of which one of the most widely used is haloperidol. One action that these phenothiazines, thioxanthenes and butyrophenones have in common is blocking of D_2 dopamine receptors (Table I).

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Dopamine and schizophrenia

The 'dopamine hypothesis' of schizophrenia (Fig. 1) predicts an increased activity of dopamine neurotransmission in the disease. The hypothesis originally developed from observations that drugs with dopamine agonist or dopamine-releasing properties (e.g. amphetamine) can induce a psychosis indistinguishable from acute paranoid schizophrenia[1]. The correlation between the clinical efficacy of antipsychotic drugs (which bind to a range of different receptors; see Table I), and their antagonist action at the D_2 dopamine receptor lends further support to the hypothesis. Moreover, post-mortem studies in the late 1970s demonstrated increased numbers of D_2 receptors in brain tissue from schizophrenic patients; however, recent positron emission tomography (PET) imaging studies have shown that D_2 receptor upregulation does not occur in young, untreated schizophrenic

EXHIBIT 3

Box 1

Schizophrenia: symptoms and pathology

Schizophrenia is a common disorder likely to affect almost 1% of the population. It is partly genetically transmitted as demonstrated by a concordance of 40–50% between monozygotic twins. Schizophrenia is a psychiatric disease with no objective physiological or biochemical diagnostic tests. In the past this has meant that the frequency and scope of diagnosis has varied according to social or individual whim, although it has improved with the increasing application of standardized diagnostic criteria. Key symptoms include hallucinations (particularly 'hearing voices'), delusions and abnormal experiences, such as the feeling that control of one's thoughts has been lost, perhaps to some outside agency. The patient loses empathy with others, becoming withdrawn and demonstrating inappropriate or blunted mood. Within this general syndrome several subtypes have been described including paranoid, residual or disorganized schizophrenia; these reflect differences in the relative patterns of symptoms but have not proved to be of much value in understanding their relationships to changes in the brain.

The distinction between two syndromes in schizophrenia is of more interest in this respect[1]. Patients having primarily positive symptoms (delusions, hallucinations, incongruous affect) have been described as type I, while those with negative symptoms (withdrawal, loss of drive, flattened affect) have the type II syndrome. There is still some dispute as to whether these subtypes relate to distinct disease processes or whether, at the other extreme, they are different expressions of a single disorder. Positive symptoms respond much better than negative symptoms to classical antipsychotic drugs. Conversely, identifiable abnormalities of brain structure have been associated more often with negative, than with positive, symptoms.

Certainly, there are structural differences in the brain in schizophrenia (recently reviewed by Roberts[2]). Schizophrenic patients tend to have smaller brains with larger ventricular volumes, reflecting relative deficits of neurons. Recent magnetic resonance imaging and postmortem morphometric studies strongly indicate that regions of the medial temporal lobe (hippocampus, amygdala and hippocampal gyrus) are particularly affected, with diminished numbers and/or disorganization of groups of neurons. These neuronal abnormalities are often more apparent in the left hemisphere. As well as morphological indications, there are also neurochemical correlates of neuronal deficits in temporal lobe structures, particularly the hippocampus. For example, a marker for GABA neurons that binds to GABA uptake sites is diminished in this region in schizophrenia[3], as is the neuropeptide CCK[4], also found in GABA-releasing neurons[5]. Losses of glutamate receptors have also been reported[6] and, parallelling the neuropathology, these abnormalities often appear to be greater in the left hemisphere.

Imaging studies of neural activity by measurement of blood flow or energy metabolism, sometimes in combination with neuropsychological tasks, have indicated the frontal cortex as another site of dysfunction in schizophrenia[7]. Neurochemically there have been reports of an increase in both pre- and postsynaptic markers of glutamate-releasing neurons in the frontal cortex[8,9]. However, these increases are not easy to understand in terms of the report of diminished numbers of neurons in some layers of the frontal cortex[10]. Nevertheless, the correlation of certain frontal[11] and temporal lobe[12] abnormalities with, respectively, negative and positive symptoms in schizophrenia provides a clear link between symptomatology and pathology in the disease.

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patients[2], and is now generally accepted to be a response to drug treatment.

The action of antipsychotic drugs in treating schizophrenia may not be simply a postsynaptic blockade of hyperactive dopamine systems; receptor blockade occurs within hours while most symptoms usually improve over a period of weeks. This temporal discrepancy has been proposed to be linked to drug-induced changes in dopamine metabolism; dopamine turnover increases but, after continued antipsychotic drug treatment, tolerance develops and dopamine metabolism returns towards normal. This effect varies between different brain regions, with the greatest tolerance developing in the amygdala and the least in the frontal cortex[3]. Thus it has been suggested that the continued increase in frontal cortical dopamine metabolism is important for the antipsychotic effect[4]. However, the opposite argument has also been postulated: the reversal of the increase in dopamine metabolism in the amygdala, a temporal lobe region that receives substantial dopaminergic innervation, might relate to the antipsychotic response[5]. This would be consistent with the observation that a decrease in plasma concentrations of the dopamine metabolite homovanillic acid, which derives in part from sub-cortical brain dopamine, correlates with clinical response to drug treatment[6].

Other evidence, particularly from post-mortem studies, also implicates regions of the temporal lobe in schizophrenia. Deficits of inhibitory and excitatory amino acid transmitter systems occur in the temporal lobe (see Box 1) as well as an abnormality in dopamine systems – an increase in dopamine concentrations in the amygdala, occurring primarily in the left hemisphere[7]. Although some of these neurochemical changes could be induced by drug treatment, there are indications that many are related to neuronal deficits. Thus the correlation

TABLE I. Common antipsychotic drugs and their typical pharmacological profiles

Chemical class	Examples	Approximate K_d values at different receptor subtypes					
		D_1 dopamine	D_2 dopamine	α_1-Adrenoceptor	H_1 histamine	5-HT_2	Muscarinic acetylcholine
Phenothiazines	chlorpromazine fluphenazine thioridazine	10–100 nM	1–20 nM	~10 nM	~10 nM	2–25 nM	20–2000 nM
Thioxanthenes	clopenthixol flupentixol	1–10 nM	~10 nM	~10 nM	~100 nM	1–10 nM	~1000 nM
Butyrophenones	haloperidol	400 nM	6 nM	6 nM	2000 nM	30 nM	$>10^{-5}$ M
Diphenylbutyl-piperidines	pimozide	200 nM	1 nM	40 nM	$>10^{-5}$ M	6 nM	1000 nM
Dibenzazepines	clozapine	300 nM	100–200 nM	10 nM	3 nM	4 nM	12 nM
Substituted benzamides	sulpiride remoxipride	$>10^{-5}$ M	10–100 nM	$>10^{-5}$ M	$>10^{-5}$ M	>1000 nM	$>10^{-5}$ M

found[8] between the loss of hippocampal GABA neurons and the increase in dopamine in the left amygdala implies that the neurons lost in schizophrenia could have regulatory effects on dopamine systems. Such an interpretation is highly speculative but provides a much needed mechanism whereby dopamine antagonist drugs might ameliorate some of the consequences of neuronal deficits in schizophrenia[9].

Side-effects and other problems

Extrapyramidal side-effects of antipsychotic drugs are due to dopamine receptor antagonism. However, actions at other receptors are also involved in the wide range of clinical effects of these drugs, some of which are listed in Box 2. Not all of these effects are deleterious. Some drugs, such as thioridazine, have reasonably high affinity for muscarinic acetylcholine receptors and are inherently less likely to induce extrapyramidal side-effects[10]; indeed parkinsonian side-effects are usually treated with muscarinic receptor antagonists.

Two major factors govern the search for novel antipsychotics. One is the need for an effective treatment for schizophrenia without the unpleasant side-effects that also decrease compliance. The second is the problem that a substantial proportion (~30%) of schizophrenic patients fail to respond to classical antipsychotic drug treatment, and many more respond only partially. Negative symptoms are particularly resistant to classical drug therapy (see Box 1). Pharmacological research and development have taken two main directions in response to these problems. Initially, attempts were made to identify compounds

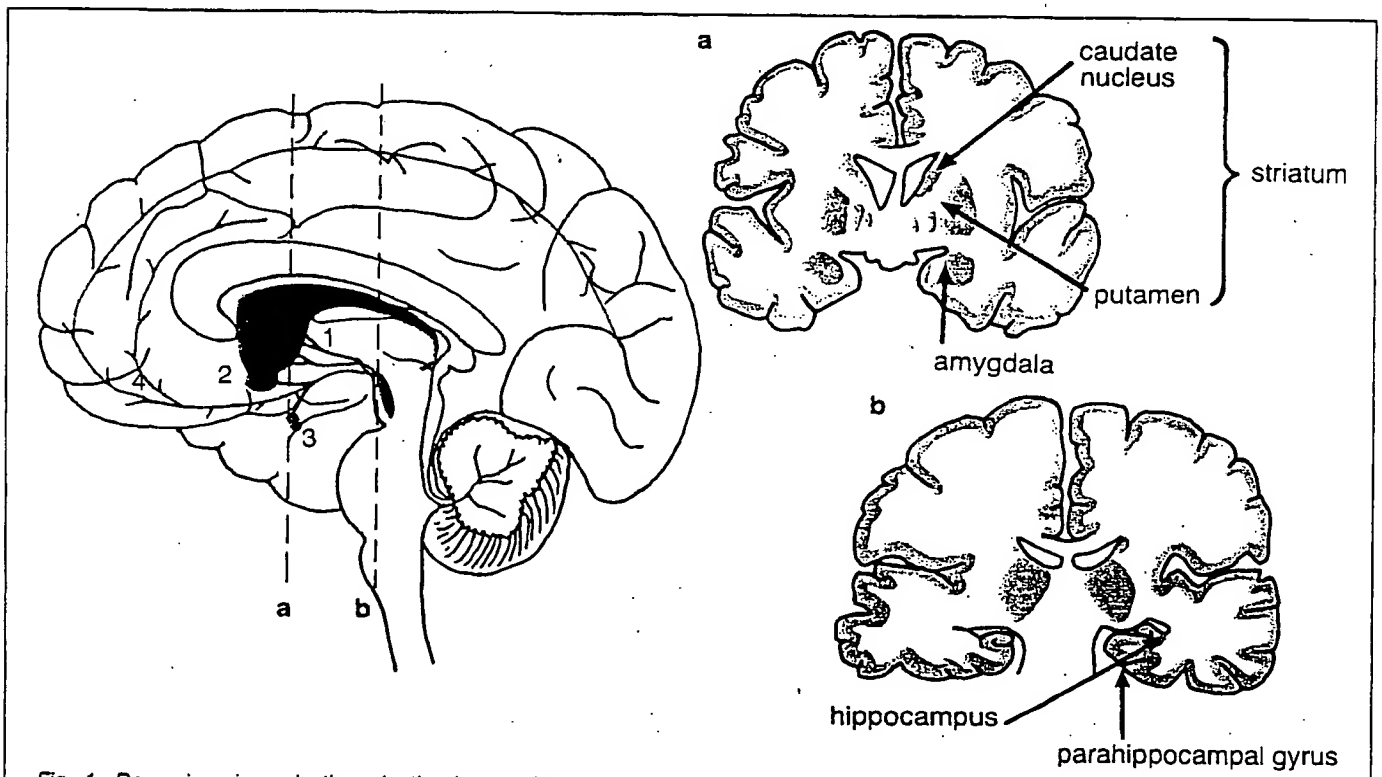

Fig. 1. Dopaminergic projections in the human brain and their topographical relationship with sites implicated in schizophrenic neuropathology. **Left:** *midline view of dopamine projections* **(dark grey)** *to:* **1**, *striatrum;* **2**, *nucleus accumbens;* **3**, *central and lateral amygdala;* **4**, *cortex.* **a** *and* **b** *indicate where the coronal sections* **(right)** *are taken.*

with a specific and selective action on dopamine systems to avoid side-effects. A second approach recognizes that actions at receptors other than those for dopamine may contribute to, and extend, the antipsychotic effect and may also provide some protection from side-effects.

Sulpiride, a D_2-selective antipsychotic

Sulpiride was one of the first drugs to offer a spectrum of action that differed from the classical antipsychotics. It is effective in some, but not all, of the animal behavioural indicators of antipsychotic action[11]. Thus catalepsy, which is induced readily by other drugs and which reflects a blockade of striatal dopamine receptors, develops only weakly with sulpiride, successfully predicting the relatively low incidence of parkinsonism associated with sulpiride that has been found in the clinic. Sulpiride has high selectivity for dopamine D_2 receptors (Table I) and is therefore free from some of the side-effects mediated by other receptors.

The differences between sulpiride and the phenothiazines and butyrophenones have led to sulpiride being described as 'atypical'. This term is now applied to any new potential antipsychotic and implies, often misleadingly, a lower incidence of extrapyramidal and other side-effects. Sulpiride and a few other atypical antipsychotics have, however, an interesting specificity in their action on different dopamine pathways in the brain. While the classical antipsychotics will, after chronic administration, inhibit the activity of most dopaminergic neurons in the brain stem, atypical drugs only inhibit the cells of the ventral tegmental area that innervate the limbic and cortical brain[12]. The neurons of the substantia nigra projecting to the striatum (which mediate extrapyramidal movement disorders) are less affected. The mechanisms involved are unclear, probably involving differences in the feedback control of these two groups of dopaminergic neurons, although recent work has cast doubt on the validity of such electrophysiological studies as a model of dopaminergic activity[13].

Other drugs that interact with dopamine have been investigated as potential antipsychotics. Partial postsynaptic agonists and/or autoreceptor agonists such as BHT920 have more subtle effects than D_2 receptor antagonists, and may provide a means of modulating dopamine systems without inducing extrapyramidal symptoms. Clinical effects of some of these drugs have been disappointing, however, and interpretation of results is confused by some lack in specificity for dopamine receptors[14].

Clozapine and D_1 blockade

Recent developments in potential antipsychotic treatments owe much to the pharmacology and clinical efficacy of clozapine (reviewed in Ref. 15). This drug was withdrawn shortly after its introduction as an antipsychotic in the 1970s following several fatalities due to drug-induced agranulocytosis. However, as clozapine treatment is associated with a low incidence of extrapyramidal side-effects, a notable lack of tardive dyskinesia and an efficacy in otherwise unresponsive patients, it has recently been reintroduced in several countries, along with regular haematological monitoring of the patient. In contrast to sulpiride, clozapine has higher affinity for 5-HT_2, histamine and muscarinic acetylcholine receptors and α-adrenoceptors than for dopamine sites. This does not preclude an antagonist action at dopamine receptors from contributing to its antipsychotic action, but PET studies show that *in vivo* it occupies only ~50% of D_2 sites, somewhat lower than the 80% occupancy exhibited by classical antipsychotic drugs[16].

By contrast, clozapine's occupation of dopamine D_1 receptors is higher than any other antipsychotic *in vivo*. Selective D_1 antagonists, such as SCH23390, are effective in certain animal models considered predictive of antipsychotic potency, and this has led to their development for the treatment of schizophrenia. Whether such drugs are less likely to induce side-effects such as parkinsonism and tardive dyskinesia has, however, been questioned[17]. Nevertheless it is conceivable that, with clozapine and other mixed D_1/D_2 antagonists, the synergism known to exist between D_1 and D_2 receptors[18] sponse to be achieved below the threshold for extrapyramidal effects. Alternatively, clozapine's potent antagonism of muscarinic receptors may prevent the inhibition of nigrostriatal cell firing that, as mentioned above, is seen with the classical antipsychotics and that may relate to these dopamine-mediated side-effects.

Clozapine and 5-HT_2 receptors

5-HT_2 receptors are found in many brain regions and mediate a variety of behaviours, some of which have been equated with psychosis[19]. However, there is no evidence that antipsychotic action can be mediated solely by 5-HT_2 receptor blockade. Clozapine has a higher affinity for 5-HT_2 receptors than for the D_2 receptors, and causes a rapid downregulation of 5-HT_2 sites[20]; this occurs with many antidepressant drugs and may contribute to clozapine's antidepressant effects.

At present, the only clinical indication for clozapine is for treatment of schizophrenic patients who do not respond to classical antipsychotics; ~50% of such patients demonstrate an improvement after six months treatment with clozapine. A role for 5-HT_2 receptor antagonism in this effect is unproven. However, other 5-HT_2 receptor antagonists have been investigated in schizophrenia, particularly for their ability to relieve negative symptoms. Risperidone, a new drug with both 5-HT_2 and D_2 antagonist potency, does indeed have effects on both positive and negative symptoms in schizophrenia[21]. In addition, a reduction of extrapyramidal symptoms during concurrent administration of 5-HT_2 antagonists and classical antipsychotics has been observed, although experimental studies have failed to identify a basis for this in terms of modulation of dopamine system activity by antagonism of 5-HT_2 receptors[22]. However, chlorpromazine is a potent 5-HT_2 antagonist, which argues against effects at this site being solely responsible for certain atypical responses.

5-HT_3 receptors

The 5-HT_3 receptor has also attracted interest for the development of potential new antipsychotics[23]. In the CNS, 5-HT_3

Common side-effects of drug treatment for schizophrenia

Acute extrapyramidal symptoms

Parkinsonism Akinesia, tremor and rigidity relating to D_2 receptor blockade; commonly treated by acetylcholine receptor antagonists although, like other extrapyramidal side-effects, it will often respond to lowering the dose of antipsychotic drug.

Akathisia 'Restless legs syndrome' is also related to high D_2 receptor occupancy, but responds to β-adrenoceptor antagonists or benzodiazepines.

Dystonia Strictly refers to sustained tonic muscular contractions, although acute dyskinesias may also be described as dystonic reactions. Dystonia is more frequent in young males than other patient groups, and is probably related to increased dopamine release following initial D_2 receptor blockade. Treated by monoamine-depleting drugs (tetrabenazine) or nicotinic acetylcholine receptor antagonists.

Tardive dyskinesia Abnormal movements, particularly of the face and tongues, but may also be of the trunk and limbs, usually appearing after chronic antipsychotic treatment with a prevalence of ~30%. Older patients are at greater risk. Drug withdrawal often results in an initial exacerbation of these dyskinesias. The neuronal basis of tardive dyskinesia remains obscure. Drug-induced increases in D_2 receptor density have been proposed responsible; however, neither post-mortem studies nor *in vivo* PET imaging have provided support for this hypothesis. A better model is that provided by Huntington's disease in which a loss of GABA-releasing neurons is fundamental to the production of abnormal dyskinetic movements. Decreases in markers for such neurons have been identified in both animal models[1] and post-mortem studies[2] of tardive dyskinesia. There is no established treatment, but there have been recent suggestions that sulpiride or clozapine ameliorate dyskinesias (as well as being associated with lower incidence), as reportedly does vitamin E treatment[3].

Weight gain A much-overlooked side-effect affecting one third of patients. The mechanism has not been adequately investigated, but probably involves hypothalamic 5-HT receptor inhibition.

Amenorrhoea and galactorrhea Absence of menstruation and excessive lactation are two of the effects of drugs on the transmitter control of hypothalamic–pituitary function, the former possibly relating to inhibition of the release of follicle-stimulating and luteinizing hormones, the latter an effect on the dopamine control of prolactin release.

Sedation Induced particularly by drugs acting at α_1-adrenoceptors and histamine receptors.

Postural hypotension A peripheral effect of α_1-adrenoceptor blockade.

Other autonomic effects Include decreased salivation, constipation and poor visual accommodation, which reflect muscarinic receptor antagonism by some of the phenothiazines.

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receptors occur in high densities only in parts of the brain stem associated with the emetic response, although higher levels are found in the hippocampus and amygdala than most other brain regions. Clozapine, but few other antipsychotics, binds to these receptors, albeit with relatively low affinity ($K_d = 1\ \mu M$)[24]. Ondansetron, the first selective 5-HT_3 antagonist to be available clinically, has been proposed to be of value for many psychiatric problems on the basis of its behavioural effects in various animal models and its interactions with neuronal systems in the limbic brain. For example, ondansetron reportedly has inhibitory effects on limbic dopamine hyperfunction in rats, an indication of potential antipsychotic efficacy[25]. Unfortunately, the clinical data have not been encouraging; the results from a large, if poorly designed, multicentre trial of ondansetron in schizophrenia have been unable to provide convincing evidence of its value as an antipsychotic[26].

Noradrenaline systems

Originally proposed 20 years ago, the suggestion that an abnormality of noradrenaline transmission underlies schizophrenia was based on the role of noradrenergic systems in central reward pathways[27]. Thus a deficit in noradrenaline neurotransmission could lead to loss of drive and anhedonia, a model for the negative symptoms of schizophrenia. Clozapine stimulates noradrenergic neuronal activity, but there is little to implicate noradrenaline in antipsychotic drug action. The evidence for a primary noradrenergic dysfunction in schizophrenia is also unconvincing, although noradrenaline may be involved in schizophrenic symptomatology[28].

Sigma site

One receptor that has recently attracted interest as a target for antipsychotic action is the haloperidol-sensitive σ site, which may mediate the psychotogenic activity of certain benzomorphans[29]. The role in brain function of this receptor, originally confused with the phencyclidine-binding site on the NMDA glutamate receptor complex, is unclear. As well as haloperidol, some of the clinically effective phenothiazine drugs have an affinity for the σ site in the submicromolar range, and many of the recently developed antipsychotics (but not clozapine) also have significant potency[30]. Thus remoxipride, another recently introduced, effective antipsychotic with a lower incidence of side-effects than haloperidol, is relatively selective for the σ site and D_2 receptors[31]. Several antipsychotic σ site ligands (e.g. tiospirone) are also antagonists of D_2 and other CNS receptors[30]; there is little to indicate that binding to the σ site alone contributes substantially to antipsychotic efficacy.

Dopamine D_3 and D_4 receptors

Most recently, molecular biology has provided a new perspective on antipsychotic drug action.

A dopamine D_3 receptor has been identified in limbic areas of the brain[32]. Since its pharmacology resembles that of the D_2 receptor, the D_3 receptor may be more important in mediating antipsychotic drug action; although its expression levels are very low. Two further dopamine receptors have also been identified. The D_4 receptor[33] resembles the D_2 and D_3 molecules with ~40% homology, while D_5 is more closely related to D_1. As well as being expressed in regions that include the amygdala and frontal cortex, D_4 has a 15-fold greater affinity for clozapine than has the D_2 site, while other antipsychotic drugs generally have a preference for D_2. If the D_4 receptor is important in human brain function, it offers great potential for D_4-selective antagonists in the treatment of schizophrenia.

Glutamate systems

The recent increasing interest in the glutamate system as 'a new target in schizophrenia'[34] stems from several observations. One is the psychotomimetic effect of phencyclidine. Phencyclidine is considered to produce a better human model of schizophrenia than amphetamine, since it induces negative symptoms in addition to an acute psychosis of primarily positive symptoms. These behavioural effects of phencyclidine are due, at least in part, to its ability to block the ion channel associated with the NMDA receptor. If antagonist action at this site is psychotogenic, it is conceivable that schizophrenia might relate to a dysfunction of glutamate transmission. And indeed there is evidence for this from postmortem studies, particularly in the frontal cortex (see Box 1). Furthermore, there is a close interrelationship between glutamate and dopamine systems; Carlsson and others have constructed elegant proposals for a dysfunction of this relationship in schizophrenia[35,36], providing a mechanism for the efficacy of dopamine antagonists in ameliorating a disorder in glutamate transmission.

Glutamate receptors, and particularly the NMDA subtype, offer a novel approach to the development of potential treatments for schizophrenia. These receptors transmission[37], being facilitatory in subcortical regions but inhibitory in the frontal cortex, the brain region most implicated in the negative symptoms of the disease. Several antipsychotics, and particularly clozapine, can block animal behaviours mediated by antagonists at NMDA receptors[38], although it is not known whether such effects contribute to clinical antipsychotic efficacy. This receptor complex has several sites open to pharmacological influence. Some noncompetitive glutamate antagonists bind to a site at which glycine has a positive modulatory effect. One such compound is HA966, which inhibits the behavioural and biochemical effects of amphetamine and phencyclidine in activating the mesolimbic dopamine system, without affecting dopamine function in unstimulated animals[39]. Although a long way from a clinical response, this finding is exciting for development of novel antipsychotics.

With this interest in glutamate systems as target sites for the treatment of schizophrenia, the gap is being bridged between psychopharmacology and the recent advances in neurochemical and pathological research into the disease. Thus antipsychotic drug development is finally moving towards more rational approaches to the treatment of this complex disorder.

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HA966: 1-hydroxy-3-amino-pyrrolidin-2-one
SCH23390: 7-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-bezazepine-7-ol
BHT920: 6-allyl-2-amino-5,6,7,8-tetrahydro-4*H* thiazolo-[4,5-d]-azepine